

REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 33-69 will be in the application subsequent to entry of this Amendment.

Information Disclosure Statement

The examiner is reminded to consider the IDS filed December 28, 2009 (after the mailing date of the current Action) for which the relevant fee was paid.

Specification

The examiner has objected that the trademarks CSY 21® and Alexa Fluor 594™ should appear in capital letters throughout the specification. Above the appropriate amendments to the text have been made to overcome this objection.

New Claims

New claims 65-69 have been added which are directed to preferred aspects of the disclosure such as the reagent, analyte, analyte binding agent and analyte analogue. Claim 65 finds basis in a page 10 lines 3-5 and the structure of HMCV-3 regarding R¹ and R², claims 51 and 53 and page 10 line 26 to page 11 line 2 regarding R³, claim 33 and the structures of HMCV1-3 regarding R⁴⁻⁹, page 10 line 21 regarding R¹⁰⁻¹⁵, and claims 37 and 38 for the coupling of the donor and acceptor. Claim 66 finds basis in page 2 lines 26-27, claim 67 is equivalent to claim 41, claim 68 is equivalent to claim 39 and claim 69 is equivalent to claim 54.

Claim Rejections – 35 USC 112

The Examiner has objected that claims 33-54 contain subject matter not described in the specification in such a way as to reasonably convey to the skilled person that the inventors had possession of the invention at the time of filing. Applicants disagree.

Firstly, the Examiner objects that the breadth of definition of the reagent is not supported by the description and that the number of examples provided is insufficient to demonstrate that the applicant was in possession of the genus at the time of filing.

Claim 33 has been amended to recite that at least one of R¹⁰-R¹⁵ is O-alkyl, based on the description at page 10 lines 11-12.

The Examiner will appreciate that one of the purposes of the present invention, as set out in the introduction, is to provide a reagent for use in detection of an analyte in a method relying on FRET. In order for FRET to occur, it is necessary for two dye species to be sufficiently close

that the electronic energy of the excited state of one species (the donor) may be transferred to the second species (the acceptor) to cause fluorescence. For this transfer of energy to take place, it is necessary that the absorption spectrum of the acceptor overlaps with the fluorescence emission spectrum of the donor.

The present inventors have determined that carbenium ion dyes as set out in the present invention are suitable for use as acceptors in FRET assays. In addition, the inventors have shown that the use of an O-alkyl group in at least one of the positions R¹⁰ to R¹⁵ is preferred. This is said at page 31 lines 8-11 of the application to be because *ortho*-substituents on the aromatic moieties shield the positive carbon center from degradation processes such as reductive or nucleophilic attack. Electron-donating species, of which O-alkyl groups are an example, will increase such stabilization of the positive charge at carbon. The skilled man will understand that this effect would be achieved by any reagent falling within the scope of amended claim 33, especially as three such compounds are exemplified in the application.

The substitution pattern at the meta and para positions of the aromatic rings will be of less importance in stabilizing the carbenium center, and thus can be a much wider range of groups, as set out in claim 33. The skilled man can select these groups to tailor the absorption spectrum of the dye acceptor to overlap with the desired donor. It is known that the substitution of aromatic rings with different groups can affect the position and breadth of the absorption band of the UV-vis spectrum, and so the skilled man can select from the range of groups set out in the claim for these positions in order that it will overlap with the fluorescence emission spectrum of the chosen donor dye. This would be a matter of routine experimentation by the skilled man. The skilled man, who is acknowledged by the Examiner to be highly skilled, such as a PhD synthetic chemist, is of course well aware of the standard methods of providing different substituents on an aromatic ring, as set out in any textbook.

Thus, the skilled reader would understand that the inventors had possession of the claimed invention at the time of filing.

The Examiner has objected that the term "analogue" is too broad to have sufficient description in the specification.

Applicants submit that the term "analogue" cannot be read in isolation in the claims in which it appears. In claim 38, it is made clear that the analyte analogue must be capable of

binding to the analyte binding agent, but that that binding must be disruptable by the analyte. This significantly limits the number of compounds that the analyte analogue may be. Further, it provides guidance to the skilled man to determine a suitable analyte analogue for his selection of analyte binding agent and analyte. It is a trivial matter for the skilled man to trial analyte analogues to arrive at the most advantageous combination for the analyte he wishes to detect.

Further, it should be noted that, while the invention has been made in the context of the detection of glucose, and thus specific examples of glucose binding agents and glucose analogues are given, it is clear that the dyes of the invention may be applied to the detection of any other analyte by FRET. The skilled man wishing to apply the invention to another analyte will be aware of suitable binding agents and analyte analogues that would be likely to work for that particular case, and so does not require specific guidance from the inventors of the present invention. That is the skilled man's general knowledge. The present invention needs only to teach the skilled man regarding the form of reagent to be used. As FRET assays in general are well known in the art for a number of target molecules, that knowledge can be used by the skilled man to substitute the compounds of the present invention for the donor moiety used in prior art assays.

The Examiner states at the bottom of page 6 of the office action that "There is no disclosure related to acceptors and donors that are covalently coupled. There is no disclosure related to any molecules wherein the phenyl rings are linked by bridging groups".

As we have discussed above, there is a discussion on pages 3 and 4 of the specification, and at page 9 lines 3-15, of the use of "molecular beacons". It is perfectly clear from these passages of the specification that this is a situation in which the donor and acceptor are covalently coupled, and so the Examiner's assertion is incorrect.

Further, the Examiner has repeatedly stated that "one or more of the R groups can form bridging groups between rings". This is not the case. The claim states that the pairs of R groups that can form bridging groups are R⁴ and R¹⁰, R⁵ and R¹¹, R⁶ and R¹², R⁷ and R¹³, R⁸ and R¹⁴, and R⁹ and R¹⁵. Each of these pairs of groups is located on the *same* phenyl ring. Thus, there are no bridging groups formed between rings. The bridging groups referred to in the claim would result in a second ring fused to the phenyl ring adjacent the carbenium ion center, but would not link one phenyl ring to another.

The Examiner states that “‘Analog’ is not defined in the specification and so is is not clear how it is related to glucose, dextran or polynucleotide linkers or what is meant by ‘analog’”. The Examiner appears to be confusing different analogues as the Examiner persists in separating the word “analogue” from its context. With regard to analyte analogues, as we have explained above, this term is defined in terms of function in claim 38. Further, it is clear from the description (see page 2 line 26 to page 3 line 3) that where glucose is the analyte, dextran is a suitable analyte analogue, and so the relationship between the term ‘analogue’ and glucose and dextran is perfectly clear. With regard to polynucleotide analogue sequences, this term is well known in the art to describe a sequence that behaves in the same way as a given polynucleotide sequence in terms of its binding to other polynucleotides, but which has backbone modifications to tailor its properties, such as for example the ease of cleavage of the backbone by enzymes. Applicants point out to the Examiner that a search of PubMed for the phrase “polynucleotide analogue” gives 1076 hits. Applicants therefore submit that this expression is perfectly clear to the skilled reader.

The Examiner has objected that claims 1-54 are rejected as unclear. Counsel presumes that the Examiner’s reference to claim 1 should in fact be to claim 33. To address the Examiner’s objection to claim 1 (33), the word “general” has been deleted from claim 33.


The Examiner has objected that the presence of a trademark name (Alexa Fluor 594) in claim 54 is unclear. There is a large range of Alexa Fluor dyes, having absorption peaks at different wavelengths. Alexa Fluor 594™ absorbs at 594 nm and fluoresces at 620 nm, as stated in the description at page 5 lines 19-21. Claim 54 is above amended to recite these features of the dye and the trademark name is removed. New claim 69 has identical wordings. We therefore submit that this definition is clear.

Reconsideration and favorable action are solicited. Should the examiner require further information, please contact the undersigned.

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Respectfully submitted,

NIXON & VANDERHYE P.C.

By: 

Arthur R. Crawford
Reg. No. 25,327

ARC:eaw
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100